The effect of physical training on hormonal status and exertional hormonal response in patients with chronic congestive heart failure

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Background  Physical training improves exercise capacity in patients with chronic heart failure. It decreases plasma noradrenaline at rest, which may be prognostically favourable. The effect on atrial natriuretic peptide, another prognostic factor, and on catabolic and anabolic hormones remains unknown. Furthermore, to our knowledge, the contribution of exertional hormonal responses to the improved exercise capacity has not been evaluated.

Methods  27 patients with stable chronic heart failure (New York Heart Association class II–III) were randomized to training (n=12) and control (n=15) groups. The training group exercised on a bicycle ergometer for 30 min three times a week for 3 months. The load corresponded to 50–60% of their peak oxygen consumption. For the next 3 months they exercised at home according to personal instructions. The control group did not change its physical activities. The levels of hormones regulating the cardiovascular system and metabolism were determined at rest and after graded maximal exercise and during exercise with constant submaximal workload.

Results  Submaximal exercise capacity increased significantly and peak oxygen consumption tended to improve by 12% in the training group. The plasma noradrenaline at rest tended to decrease by 19%. The plasma level of N-terminal pro atrial natriuretic peptide did not change. Serum cortisol, a catabolic hormone, was normal at baseline and remained unchanged. The serum levels of anabolic hormones, growth hormone and insulin, as well as dehydroepiandrosteronesulfate and free testosterone were within a normal range at baseline. They were not altered by training. The dehydroepiandrosteronesulfate/cortisol, and the free testosterone/cortisol ratios, reflecting anabolic/catabolic balance, did not change, either. Training resulted in a higher peak noradrenaline response during graded maximal exercise. The rise in serum cortisol during exercise tended to attenuate.

Conclusion  Physical training, which improves exercise capacity, does not have an unfavourable effect on anabolic/catabolic balance or neurohumoral activation in patients with congestive heart failure. It decreases plasma noradrenaline at rest. Minor changes in hormonal responses during exercise emerged after physical training which unlikely contribute to the improved exercise capacity.

Key Words: Anabolism, catabolism, congestive heart failure, hormones, physical training.

Introduction  Chronic congestive heart failure is characterized by increasing neurohormonal activation which contributes to the deterioration of the syndrome. This has an unfavourable prognostic significance[1,2]. On the other hand, an imbalance of anabolic and catabolic factors with increased cortisol, tumour necrosis factor-α, adrenaline and noradrenaline levels has been described in cachectic but not in non-cachectic congestive heart failure patients. Cachexia is more closely associated with hormonal changes in congestive heart failure than symptoms, exercise capacity and left ventricular function[3].

Other groups, and our own, have previously shown that physical training improves exercise capacity and reduces symptoms in patients with congestive heart failure[4–8]. Studies show that noradrenaline levels at rest and during submaximal exercise are decreased by physical training[5,7]. To our knowledge, no published
data on the effect of physical training on other anabolic or catabolic factors in patients with congestive heart failure exist.

It is well known that hormones greatly influence skeletal muscle metabolism by modifying the circulation and energy supply from carbohydrates and lipids. The hormonal and metabolic response during exercise in patients with congestive heart failure has been reported to be similar to that in healthy individuals[9], but the influence of physical training upon hormonal response during exercise has not been previously studied, as far as we know.

We performed a controlled and randomized study to evaluate whether physical training of moderate intensity affects the anabolic/catabolic balance in patients with congestive heart failure, and how this training affects plasma N-terminal pro atrial natriuretic peptide (Nt-proANP), another prognostic hormone. Secondly, we examined whether the exertional response of the hormones regulating the cardiovascular system and metabolism contribute to the improved exercise capacity achieved by physical training. We have previously reported the effect of physical training on exercise capacity based on the same patient material[8].

Methods

Patients

Twenty-seven patients, under 65 years of age, with a history of symptomatic congestive heart failure, longer than 6 months, were randomized to a training (n=12) and control group (n=15). They were in NYHA functional classes II (n=15) or III (n=12) with a left ventricular ejection fraction under 40%. The aetiology of congestive heart failure was either idiopathic dilated (n=18) or ischaemic (n=9) cardiomyopathy. The diagnosis and aetiology were confirmed with a clinical examination together with a cardiac ultrasound study and right heart catheterization. All patients with ischaemic aetiology had a history of myocardial infarction but had neither exercise-induced chest pain nor electrocardiographic evidence of exercise ischaemia. The patients had been haemodynamically stable for at least 3 months before the study. The medical regimen was kept stable. Only a change in the diuretic dose was allowed. None had a pulmonary disease or diabetes. The patients gave informed consent for this trial, which was approved by the local ethics committee.

Training

The training programme consisted of a supervised period followed by a home-based training period, both lasting 3 months. The training protocol has previously been described in detail[8]. The control patients were advised not to change their previous physical activity during the 6-month period.

Exercise test protocols

A graded maximal exercise test was performed on an upright bicycle ergometer with continuous analysis of expiratory gases according to the protocol described in detail earlier[10]. It was performed at 0900 h before the intake of the morning meal and medication. Before the exercise, blood samples were taken. A needle was inserted into a cubital vein, and the patients rested for 30 min in a supine position. While still supine, samples of plasma adrenaline, noradrenaline, cyclic adenosine monophosphate (cyclic AMP), Nt-proANP and serum cortisol, growth hormone, insulin and free fatty acids were drawn for determination of basal levels. Corresponding samples were taken immediately after cycling while the patient was still sitting on the bike.

Exercise endurance was determined by the duration of ergometer cycling at a constant submaximal workload corresponding to 85% of the peak oxygen consumption at baseline. The test was performed at 1400 h. The patients took their normal medication in the morning, and had a light lunch 3 h before the test. Samples for serum cortisol, growth hormone, insulin and free fatty acid determinations were taken before the start of the test, at the end and, in addition, after 3 and 6 months at the time point equal to the duration of this test at baseline. Samples for plasma adrenaline and noradrenaline determinations were taken at the end of the test at baseline and at the corresponding time point or, if the exercise time was shorter, at the end, after 3 and 6 months. The first four patients in the control group did not perform this test.

The two tests were performed at baseline and after 3 and 6 months. The interval between the tests was 2–4 days.

Samples for serum testosterone, sex hormone binding globulin, dehydroepiandrosterone sulfate and albumin determinations were taken at rest in the morning at baseline and after the 3- and 6-month study period. Serum free testosterone was calculated on the basis of serum testosterone and sex hormone binding globulin according to Andersson[11].

The plasma samples were stored in −70 °C and the serum samples in −20 °C.

Laboratory determinations

The following methods were used. Plasma adrenaline and noradrenaline (Tris-EGTA-DTT-plasma: Trizma base 0.5 mol l−1, ethyleneglycol-bis-N,N-tetra acetic acid 0.25 mol l−1, dithiothreitol 0.25 mol l−1): high performance liquid chromatography using the method described by Scheinin et al.[12]. The within-assay and between-assay imprecisions were 9.5 and 15.5% for adrenaline and 2.4 and 8.4% for noradrenaline,
respectively. Plasma Nt-proANP (EDTA plasma): Nt-proANP kit (Biotop, Oulu, Finland), within-assay imprecision was <10%, between-assay imprecision was <15%. Plasma cyclic AMP (EDTA plasma): 125J assay (Amersham International Inc., Amersham, U.K.), within-assay imprecision was 9·7–13·6%. Serum cortisol: Orion Diagnostica125J Radioimmunoassay Kit (Orion Diagnostica, Espoo, Finland), within-assay and between-assay imprecisions were 1·7–4·1 and 4·3–9·0%, respectively. Serum growth hormone: LSA-hGH immunoradiometric assay (CIS bio international, Gif-sur-Yvette, France), within-assay imprecision was 2·3–2·8 and between-assay imprecision 3·2–4·4%. Serum insulin: ‘Phadeseph’ kit (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden), within-assay imprecision was 4·6–9·4%. Serum free fatty acids: fluorometrically by an enzymatic method described by Shimizu et al.[13], between-assay imprecision was 12%. Serum testosterone: Testosterone 125J radioimmunoassay kit (Orion Corporation Farmos, Turku, Finland), within-assay imprecision was 7·7 and between-assay imprecision 5·2%. Serum sex hormone binding globulin: fluoroimmunometrically using ‘Delphi’ kit (Wallac Oy, Turku, Finland), within-assay and between-assay imprecisions were 1·3–1·8 and 5·1–10·1%, respectively. Serum dehydroepiandrosteronesulfate: Coat-A-Count DHEAS radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, U.S.A), within-assay imprecision was 8·2 and between-assay imprecision 8·3%. Serum albumin: bromcresol purple method described by Pinnell et al.[14], between-assay imprecision was 2·1%.

Statistics

The Mann–Whitney U test was used to compare the groups at baseline. The Wilcoxon signed rank test was used to measure the hormonal responses in single exercise tests. Repeated measures analysis of variance was used to test intra- and inter-group changes in the hormonal levels at rest and in the hormonal responses to exercise during the study period. When a significant change was detected, Fisher’s protected least significant difference was used to isolate it. The level of significance was set at \( P<0·05 \).

Results

Baseline characteristics

The baseline characteristics of the training and control groups are presented in Table 1. The groups did not differ from each other. One patient in the control group was hospitalized 1·5 months after the beginning of the study because of significant fluid retention. His data is not included in the analyses. The sex steroid data of the only woman in the study were also excluded.

Exercise capacity

Physical training significantly improved the exercise capacity and reduced the symptoms of heart failure. Exercise duration in the bicycle test with a constant submaximal workload almost doubled during the 3-month supervised training period, and the result was maintained during the home-based training period[8]. The workload in the graded maximal exercise test also improved significantly. The 12% increase in peak oxygen consumption did not reach statistical significance. No changes were observed in these parameters in the control group. The New York Heart Association functional
class improved from $2.4 \pm 0.1$ at baseline to $1.9 \pm 0.2$ after both the 3- and 6-month observation periods in the training group ($P<0.05$ vs baseline) but remained unchanged in the controls.

**Hormone levels at rest**

Factors related to the severity of congestive heart failure

Plasma adrenaline did not change in either group (Fig. 1(a)). In the training group, basal plasma noradrenaline tended to decrease from $2.53 \pm 0.34$ nmol l$^{-1}$ at baseline to $2.51 \pm 0.31$ nmol l$^{-1}$ after 3 months and $2.05 \pm 0.26$ nmol l$^{-1}$ after 6 months ($P=0.09$ vs baseline) (Fig. 1(b)). Basal plasma cyclic AMP ($P=0.09$) also tended to decrease during the study in the training group. However, when the changes in these parameters were compared between the groups, no differences were observed. Training had no effect on the plasma Nt-proANP level at rest (Fig. 1(c)).

### Anabolic and catabolic hormones

The levels of serum cortisol, growth hormone and insulin were within a normal range at baseline. Serum cortisol and insulin levels did not change in either group during the study period (Fig. 1(d,f)). Serum growth hormone levels decreased in the control group during the study period ($P<0.05$) but the change was not different from that of the training group (Fig. 1(e)). Serum albumin was normal, and serum sex hormone binding globulin, free testosterone and dehydroepiandrosteronesulfate levels were relevant for age in both groups at baseline (Table 2)\textsuperscript{15}. They did not increase or decrease during the study period. The free testosterone/
Hormone responses and levels during exercises

At baseline, the graded maximal exercise test resulted in a significant increase in the plasma catecholamine levels in both study groups (P<0.01 between rest and immediate post exercise) (Fig. 1(a,b)). The rise in plasma noradrenaline further increased in the training group during the study (P<0.05 vs baseline) (Fig. 1(b)). The rise remained unaltered in the control group, but the change did not differ significantly between the groups. Plasma cyclic AMP responded with a significant rise in both groups to exercise but no training effect was observed.

When the catecholamine levels were compared during exercise with constant submaximal workload at the time point corresponding to the exercise time at baseline, which marked an equal workload performed, both the plasma adrenaline and the noradrenaline level showed a decreasing trend in the training group during the study (P=0.14 and P=0.13, respectively vs baseline).

Plasma Nt-proANP concentration increased significantly during the graded maximal exercise test at baseline in both groups, but this exercise response was not affected by training (Fig. 1(c)).

The graded maximal exercise test resulted in a significant rise in serum cortisol and growth hormone levels in both groups (Fig. 1(d,e)). The rise in serum cortisol did not alter in either group during the study period, but tended to diverge between the groups (P=0.11 after 6 months), increasing in the controls compared to the training group. In contrast, the response of serum growth hormone increased in the training group but not significantly compared with the controls.

During the test with a constant submaximal workload, the serum cortisol level did not rise notably in either group at baseline (Fig. 2). In the control group, a significant increase in response was seen during the study (P<0.05 vs baseline), while in the training group, the response remained similar in spite of the substantially increased exercise time. After equal workloads had been performed, at the point corresponding to the cycling time at baseline, there was an increase in the serum cortisol response (P<0.05 vs baseline) in the control group with no change in the training group. During this test the serum growth hormone response did not change significantly (Fig. 2).

The serum insulin level did not change in either group during the graded maximal exercise at baseline and training had no effect (Fig. 1(f)). The serum free fatty acid level decreased in the training group at baseline (P<0.05), but the change was not different from the control group. The response was not altered in either group during the study.

The serum insulin and free fatty acid level did not change in either group during the exercise test with constant submaximal workload at baseline. The responses, corresponding to equal cycling time, did not alter during the study, either (Fig. 3). However, the total free fatty acid response during this test increased significantly in the control group during the study (P<0.05 vs baseline).

Factors related to the severity of congestive heart failure

Studies on hormones and congestive heart failure have mainly focused on neuroendocrine activation because of
its key role in pathophysiology and its prognostic significance\textsuperscript{1,16}. So far, we have no direct evidence that physical training can favourably affect the prognosis of congestive heart failure. To our knowledge, only Belardinelli et al. in their preliminary results showed that one-year training significantly reduced the composite endpoint of death, myocardial infarction and pulmonary oedema during a 2-year follow-up\textsuperscript{17}.

We found a decreasing trend in basal plasma noreadrenaline levels during the study in the training group, although the change was not different from that of the control group. Physical training has earlier been shown to lower plasma noradrenaline levels and noradrenaline spillover at rest\textsuperscript{5,7}. The reduced effect on basal noradrenaline may reflect the intensity of the training, which was essentially greater in the study of Hambrecht et al. compared with ours. The basal plasma noradrenaline levels in their study were also a little higher at baseline. In another study, low intensity physical training did not cause a significant reduction in plasma noradrenaline levels at rest\textsuperscript{6}.

The level of plasma Nt-proANP has a significant correlation with mortality in stable congestive heart failure\textsuperscript{18}. In severe heart failure, a decrease in Nt-proANP levels due to treatment may improve prognosis according to some data\textsuperscript{19}. The basal plasma Nt-proANP remained unchanged in our study. This result is shared by Coats et al.\textsuperscript{20} and is in accordance with our results that in patients with congestive heart failure physical training does not cause any alterations in cardiac volumes or pressures at rest\textsuperscript{8}, which are known to be the determinants of ANP release\textsuperscript{21,22}. The stable
Nt-proANP levels also support the view that physical training does not have a deleterious effect on central haemodynamics.

**Anabolic/catabolic balance**

Patients with congestive heart failure are at risk of developing cardiac cachexia. Physical training may increase the risk by leading to a catabolic state by increasing energy expenditure, stimulating the secretion of catabolic hormones and inhibiting insulin and testosterone secretion. On the basis of our study, that is not the case, if the patients train with moderate intensity, and if they have no signs of cachexia when the training programme begins. We used two indexes to measure the anabolic/catabolic balance, free testosterone/cortisol and dehydroepiandrosteronesulfate/cortisol ratios. Previous results from our laboratory have shown that the free testosterone/cortisol ratio is the best indicator of overstrain in healthy people[23]. The concentration of dehydroepiandrosteronesulfate, which is the major steroidal product of the adrenal gland, has less diurnal variation than dehydroepiandrosterone, whose ratio to cortisol has also been used as an index of wasting and balance between anabolism and catabolism[24,25].

As far as we know, no data exist on the effect of more intensive training in this respect, and if signs of cachexia are present the effect of physical training is still unknown. In cachectic patients with congestive heart failure, there is an increase of catabolic factors (cortisol and tumour necrosis factor-α) and a decrease of anabolic dehydroepiandrosterone[3]. Growth hormone resistance has also been described[3]. These factors can modify the effect of training and put greater requirements on planning a training programme. A randomized study in that

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*Figure 3* The levels of serum insulin and free fatty acids (FFA) in the control (left panels) and the training group (right panels) during exercise test with constant submaximal workload (85% of the baseline peak oxygen consumption) at baseline (——■——), the samples taken on the bicycle before the cycling and immediately after it, and after 3 (——△——) and 6 (——○——) months, the samples taken on the bicycle before the cycling, at the time point equal to the cycling duration at the baseline and immediately after the cycling. The total FFA response increased significantly compared to the baseline in the control group (*P*<0.05). The data are presented as mean ± SEM.
subgroup of congestive heart failure patients is clearly warranted.

**Hormonal response to exercise**

Little data on hormonal response and metabolism during exercise in patients with congestive heart failure exist. At low and moderate absolute workloads, plasma noradrenaline is higher compared with healthy people\[26,27\]. Our results show that physical training tended to lower plasma catecholamines at these working levels, which is in agreement with previous reports\[6,7\]. At peak exercise, the plasma noradrenaline response has been shown to be attenuated\[27\], although there are varying results\[8,28\]. Our finding, that physical training is associated with an increased noradrenaline response to maximal exercise, can mark a reversal of an attenuated noradrenaline response. However, this does not necessarily mean an increased noradrenaline cell effect because the exercise response in plasma cyclic AMP levels, the intracellular messenger of the catecholamines in tissues, did not change.

Our results also suggest that physical training attenuates the cortisol response during exercise. The importance of this is unclear but it is unlikely to be a major contributor to the improved exercise capacity. It may be a sign of lower exercise strain. The same training effect on cortisol response has also been shown in healthy persons\[29\].

Stronger insulin decrease and greater relative fat utilization have been seen in patients with congestive heart failure\[9,30\]. This may be due to increased noradrenaline levels at submaximal workloads and an insulin resistance resulting in higher free fatty acid levels. The lack of a training effect on free fatty acid levels during exercise suggests that moderate training of this duration does not have a significant effect on exertional lipolysis. Thus it is evident that this does not contribute to improved exercise capacity.

**Limitations of the study**

Our two groups were small because of the unforeseen difficulty in finding patients fulfilling the inclusion criteria. This was the major limitation of our study. Under these circumstances the wide variation in the hormone levels at rest and during exercise can conceal possible differences. Because of the small number of studies in the literature on the exertional response of hormones in patients with congestive heart failure, it would have been helpful to have had a group of healthy people in this study. However, some previous data on healthy persons, e.g. from our laboratory exist\[31,32\].

**Conclusion**

Physical training of moderate intensity may cause prognostically favourable hormonal changes in patients with congestive heart failure. It does not induce catabolism in non-cachectic patients. The improved exercise capacity achieved by physical training was not generated by a hormonal or metabolic factor, according to our study.

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